Impact of growth hormone therapy on adult height of children with idiopathic short stature: systematic review
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CRD summary
This review concluded that growth hormone therapy appeared to be effective in promoting growth in children with idiopathic short stature, but the effect was less than that achieved for other conditions. The conclusions should be treated with caution, due to limitations in the review, the relatively low quality of studies identified, and the observed variability in individual response to therapy.

Authors' objectives
To evaluate the impact of growth hormone therapy on the adult height of children with idiopathic short stature.

Searching
The Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE were searched up to April 2010 using keywords that were reported. The bibliographies of retrieved articles were consulted and no language restrictions were imposed.

Study selection
To be eligible, studies had to be of children with initial short stature defined as: a height more than two standard deviations below the mean. Their peak growth hormone responses had to be more than 10 micrograms per litre and they had to have not reached puberty, have no previous growth hormone therapy, and have no comorbid conditions that could impair growth. The primary outcome measure was the difference in adult height between children treated with growth hormone and those not treated. Adult height was considered to be achieved when the growth rate was less than 1.5cm per year or the bone age was 15 years for females or 16 years for males. Secondary outcomes were the height gain from inclusion in the study to adulthood and the difference between adult height and mid-parental height. Studies had to be randomised controlled trials (RCTs) or non-randomised trials.

Across the randomised trials the mean age at the start of therapy ranged from 6.1 to 12.9 years, whilst across the non-randomised trials it ranged from 7.6 years to 12.5 years. All children had not reached puberty. The daily dose of growth hormone ranged from 0.033 to 0.067mg per kg in the randomised trials and from 0.02 to 0.05mg per kg in the non-randomised trials. The mean duration of therapy was 5.4 years (SD 1.5) in the randomised trials and 5.3 years (SD 1.8) in the non-randomised trials.

It was unclear how many reviewers selected the trials for the review.

Assessment of study quality
Randomised trials were evaluated, using the Endocrine Society guidelines, and classified as high, moderate, low, or very low quality. It was unclear if the same guidelines were used to rate the non-randomised trials and it was unclear if more than one reviewer assessed quality.

Data extraction
Effect sizes were calculated, for each trial, for the mean difference between treated and untreated groups and the change from baseline to adult height, with their confidence intervals. It was unclear if more than one reviewer extracted these data.

Methods of synthesis
RCTs and non-randomised trials were pooled separately in meta-analyses, using a fixed-effect model. When the effect size was significant in the fixed-effect model, the analysis was repeated using a random-effects model. Heterogeneity was investigated using the I² statistic. Publication bias was assessed through funnel plots. Sensitivity analyses were undertaken to investigate the effects of enrolling bias.
**Results of the review**

Ten trials were included, with a total of 592 participants; three were RCTs and seven were non-randomised trials. Two RCTs were of moderate quality, whilst one was of low quality. One of the moderate-quality trials had a high dropout rate and the other had a small sample with variation in the dose of growth hormone and in the results. The low-quality RCT was small. Six of the non-randomised trials were of low quality and one was of low-moderate quality. Only one trial had a placebo control.

Randomised trials showed a pooled mean difference of 0.65 standard deviations (approximately 4cm; 95% CI 0.40 to 0.91) in adult height between the treated and untreated groups. No statistically significant heterogeneity was noted. The height gain achieved by the treated group significantly exceeded that of the untreated group, with a mean difference of 0.79 standard deviations (4.7cm; 95% CI 0.50 to 1.09). No significant heterogeneity was observed. Two RCTs corrected for mid-parental height and the mean corrected adult height of the treated group significantly exceeded that of the untreated group (0.87 SD, 95% CI 0.28 to 1.46). Significant heterogeneity was noted (I²=81%).

Non-randomised trials showed a pooled mean difference of 0.45 standard deviations (approximately 3cm; 95% CI 0.18 to 0.73) in adult height between the treated and untreated groups, with significant heterogeneity (I²=70%). The height gain achieved by the treated group significantly exceeded that of the untreated group with a mean difference of 0.71 standard deviations (5cm; 95% CI 0.42 to 0.99), with significant heterogeneity (I²=77%).

A wide individual variability in the response to growth hormone therapy was reported in all of the trials; none of them reported serious adverse effects of growth hormone therapy.

**Authors’ conclusions**

Growth hormone therapy appeared to be effective in promoting growth in children with idiopathic short stature, but the effect was on average less than that achieved for other conditions. Individual response to therapy was highly variable and further studies were needed to identify those who would respond.

**CRD commentary**

This review was based on broadly defined inclusion criteria for participants, intervention, outcomes, and study design. Searching was limited to two databases and supplemented with the bibliographies of identified articles. No language restrictions were imposed, but only published material was sought, introducing the possibility of publication bias. It was unclear if the review processes of study selection, data extraction, and quality assessment were carried out by more than one reviewer, which would help to minimise bias. A quality assessment was carried out, but trials were rated as moderate, despite fundamental flaws. It was appropriate to synthesise the results of the randomised and non-randomised trials separately as they had differing levels of bias, but there was still evidence of statistical and clinical heterogeneity.

The conclusions on the effectiveness of growth hormone therapy in this population should be treated with caution, given the limitations in the review, the quality of the included studies, and the observed variability in individual response to therapy. This review did not assess the relationship between height gain and quality of life or psychosocial outcomes.

**Implications of the review for practice and research**

**Practice:** The authors stated that practitioners and policy makers should consider the clinical importance and value of the height gained in relation to the goals of treatment, which might include physical and psychosocial well-being, adverse effects, cost of therapy, and patients’ expectations.

**Research:** The authors stated that further high-quality randomised, double-blind, placebo-controlled trials, assessing the achievement of adult height, were necessary to determine the efficacy, ideal dosage, and long-term safety of growth hormone therapy.

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